Original Article

Incidence and characteristics of biphasic and protracted anaphylaxis: evaluation of 114 inpatients

Seiro Oya, Tomoki Nakamori, and Hirohisa Kinoshita

Department of Emergency and Critical Care Medicine, Yokohama Rosai Hospital, Yokohama, Kanagawa, Japan

Aim: Anaphylaxis is a systemic allergic reaction that potentially causes death. Most anaphylactic reactions are uniphasic, but some cases may be biphasic or protracted. However, these clinical epidemiology concepts are unfamiliar in Japan. Therefore, we have investigated the incidences and characteristics of patients with biphasic and protracted anaphylaxis.

Methods: We retrospectively evaluated patients with anaphylaxis in a single emergency medical center located in Yokohama, Japan from April 2009 to March 2012. We analyzed the incidences and characteristics of patients with biphasic and protracted anaphylaxis who needed to be admitted.

Results: A total of 253 patients were diagnosed with anaphylaxis and 114 patients needed to be admitted. Of the 114 patients, 103 (90.4%) were uniphasic, 7 (6.1%) were biphasic and 4 (3.5%) were protracted anaphylaxis. The most common antigens were foods and drugs. The median onset of a biphasic reaction was 8 h and dermatologic symptoms were mostly observed. Regarding severity, mild symptoms were seen in four cases, similar symptoms to the initial reaction were seen in two cases, and only one case was severe. The duration of protracted anaphylaxis varied from 2 to 8 days.

Conclusion: The incidence of biphasic and protracted anaphylaxis in inpatients was 6.1% and 3.5%, respectively. The median onset of biphasic reaction was 8 h, and most symptoms were mild or similar to the initial reaction. We suggest that patients with anaphylaxis need an 8-h and ideally a 24-h observation period in order to monitor possible biphasic reactions. The duration of protracted anaphylaxis was up to 8 days.

Key words: Anaphylaxis, biphasic reaction, emergency department, observation period, protracted reaction

INTRODUCTION

ANAPHYLAXIS IS A systemic allergic reaction that potentially causes death. According to a previous survey, approximately 1% of emergency department (ED) visits were allergy-related and 63% of the patients were coded urgent in the USA.[1] Most anaphylactic reactions are triggered through an immunologic mechanism involving immunoglobulin E[2] and are typically uniphasic, but sometimes they are biphasic or protracted.

Biphasic reactions are characterized by a uniphasic response, followed by an asymptomatic period of 1 h or more, and then subsequent return of symptoms without further exposure to an antigen.[3] Emergency physicians are often concerned about these reactions, because they could occur after the patient has been discharged home and could be fatal. According to recent reports, the incidence of biphasic reactions varies from 1 to 23% of all anaphylactic reactions, and certain characteristics of biphasic reactions have been described in several bodies of research.[4,5] A protracted anaphylaxis lasts hours to days without clearly resolving completely, and there are some case reports of the reaction.[6] However, these clinical epidemiology concepts are unfamiliar in Japan.

The objective of this study is to investigate the incidences and characteristics of biphasic and protracted anaphylaxis occurring in Japanese ED.

METHODS

Study design and setting

WE CARRIED OUT this study in a single emergency medical center located in Yokohama, Japan. We retrospectively evaluated patients with anaphylaxis who needed to be admitted from April 2009 to March 2012. We investigated the incidence and characteristics of biphasic and protracted anaphylaxis by reviewing medical records.

Corresponding: Seiro Oya, MD, Department of Emergency and Critical Care Medicine, Yokohama Rosai Hospital, 3211 Kozukue-cho, Kohoku-ku, Yokohama, Kanagawa, 222-0036, Japan. E-mail: seiooya@gmail.com.
Received 8 Feb, 2014; accepted 20 Mar, 2014; online publication 19 May, 2014

© 2014 Japanese Association for Acute Medicine

Definition

For this study, the definition of anaphylaxis is based on three diagnostic criteria, which were approved by a multidisciplinary group of experts in 2005 and 2006.[7] Table 1 shows the criteria.

Biphasic anaphylaxis was defined as a uniphasic response, followed by an asymptomatic period of 1 h or more, and then subsequent return of symptoms without further exposure to an antigen.[3] In addition to this concept, the criteria (Table 1) were used for the second reaction as well. Regarding the severity of biphasic reactions, more than three attending physicians assessed them by comparing the reactions to the initial symptoms stated in the medical records (mild, similar, or severe). There is no concrete definition for protracted anaphylaxis. In this study, we defined the reaction as lasting at least 5 h without clearly resolving completely, in accordance with published research.[6] Etiology was determined as best as possible by history. If a clear causality could not be established, the suspected antigen was classified as unknown.

Outcome measure

Uniphasic and biphasic cases were compared regarding patient age, sex, incidence, initial symptoms and signs, initial treatment of epinephrine, corticosteroid, H1-antagonist and H2-antagonist, and clinical course.

Protracted reactions were assessed by patient age, sex, incidence, initial symptoms and signs, initial treatment of epinephrine, corticosteroid, H1-antagonist and H2-antagonist, and clinical course.

Statistical analysis

The Mann–Whitney *U*-test was used for continuous data and the Pearson χ^2 and Fisher exact tests were used for ordinal data as appropriate. All statistical analyses were carried out with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander software designed to add statistical functions frequently used in biostatistics. *P*-values of less than 0.05 were considered statistically significant.

Exclusion criteria

We excluded cardiac arrest cases because it is hard to diagnose completely based on limited clues.

RESULTS

A TOTAL OF 253 patients were diagnosed with anaphylaxis, and 114 of the cases needed to be admitted during the 3-year period. Of the 114 inpatients, 103 were

Table 1. Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

Criterion 1
Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both and at least one of the following conditions:
- A. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- B. Reduced BP or associated symptoms and signs of end-organ dysfunction (e.g., hypotonia, collapse, syncope, incontinence)

Criterion 2
Two or more of the following that occur rapidly after exposure to a likely allergen for the patient
- A. Involvement of the skin–mucosal tissue (e.g., generalized hives, itchy/flushed, swollen lips/tongue/uvula)
- B. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- C. Reduced BP or associated symptoms and signs (e.g., hypotonia, syncope, incontinence)
- D. Persistent gastrointestinal symptoms and signs (e.g., crampy abdominal pain, vomiting)

Criterion 3
Reduced BP after exposure to a known allergen for the patient
- A. Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline (in adults)
- B. Age-specific low systolic BP (in infants and children)
  - less than 70 mmHg in infants aged from 1 month up to 1 year,
  - less than (70 mmHg + (2 × age)) in children aged 1–10 years,
  - less than 90 mmHg in children aged 11–17 years

BP, blood pressure.

© 2014 Japanese Association for Acute Medicine

Table 2. Comparison of uniphasic and biphasic anaphylaxis in 110 Japanese inpatients

Comparator	Uniphasic (n = 103)	Biphasic (n = 7)	P-value
Age, years (SD)	38.7 (26.9)	31.0 (27.5)	0.49
Male sex	61 (59.2%)	3 (42.9%)	0.45
Symptoms and signs			
Skin	92 (89.3%)	7 (100%)	>0.99
Respiratory	82 (79.6%)	4 (57.1%)	0.17
Cardiac	30 (29.1%)	3 (42.9%)	0.43
Gastrointestinal	31 (30.1%)	3 (42.9%)	0.67
Treatment			
Epinephrine used	61 (52.9%)	4 (57.1%)	>0.99
Corticosteroid used	98 (95.1%)	5 (71.4%)	0.06
H1-antagonist used	102 (99.0%)	7 (100%)	>0.99
H2-antagonist used	88 (85.4%)	7 (100%)	0.59
Interval, min (SD)	79.4 (74.6)	110.7 (91.9)	0.41

Interval, interval from onset to initial treatment; SD, standard deviation.

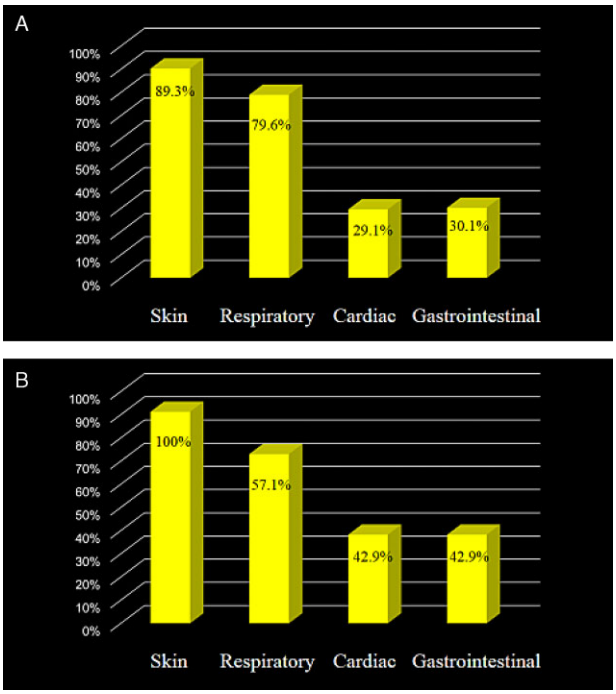

Fig. 1. Comparison of initial symptoms between (A) uniphasic and (B) biphasic anaphylaxis in 110 Japanese inpatients.

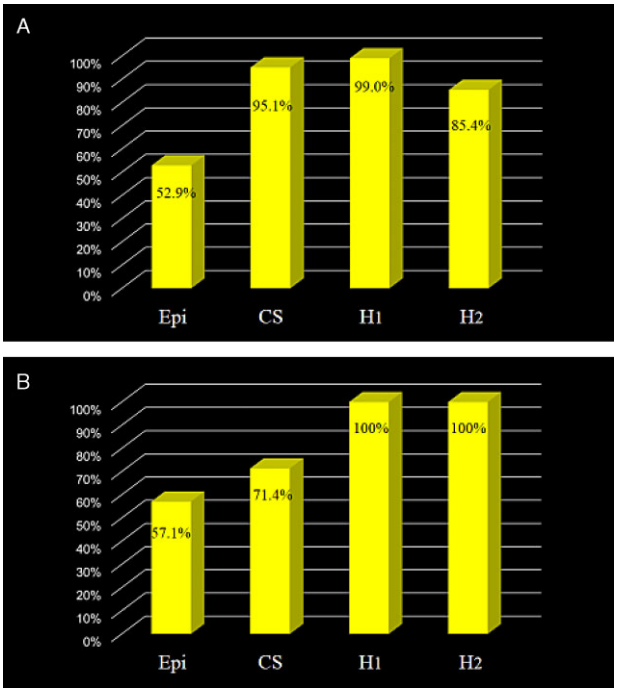

Fig. 2. Comparison of initial treatment between (A) uniphasic and (B) biphasic anaphylaxis in 110 Japanese inpatients. CS, corticosteroid; EPI, epinephrine; H1, H1-antagonist; H2, H2-antagonist.

uniphasic (90.4%), 7 (6.1%) were biphasic, and 4 (3.5%) were protracted anaphylaxis. The mean age was 38.7 years (standard deviation [SD], 26.9 years), 31.0 years (SD, 27.5 years), and 36.0 years (SD, 14.2 years), and 61 (59.2%), 3 (42.9%), and 2 (50%) patients were male in the groups with uniphasic, biphasic, and protracted reactions, respectively. Table 2 summarizes the characteristics of uniphasic and biphasic reactions. Figures 1 and 2 compare symptoms and treatments of uniphasic and biphasic reactions, respectively. Of the 114 cases, dermatologic symptoms were seen in 92 (89.3%), 7 (100%), and 4 (100%), respiratory symptoms were seen in 82 (79.6%), 4 (57.1%), and 4 (100%), cardiac symptoms were seen in 30 (29.1%), 3 (42.9%), and 2 (50%), and gastrointestinal symptoms were seen in 31 (30.1%), 3 (42.9%), and 1 (25%) in patients with uniphasic, biphasic, and protracted reactions, respectively.

The most common antigens were foods (73 [70.9%], 3 [42.9%], and 2 [50%] of cases), followed by drugs (20 [19.4%], 3 [42.9%], and 2 [50%] cases) in uniphasic, biphasic, and protracted reactions, respectively. Bees were involved in 3 uniphasic reactions and 1 biphasic reaction, and 2 cases of food-dependent, exercise-induced anaphylaxis were seen in uniphasic anaphylaxis. There was no case of hereditary angioedema.

In terms of initial treatment, epinephrine was given in 61 (59.2%), 4 (57.1%), and 3 (75.0%), corticosteroids in 98 (95.1%), 5 (71.4%), and 4 (100%), H1-antagonist in 102 (99.0%), 7 (100%), 4 (100%), and H2-antagonist in 88

© 2014 Japanese Association for Acute Medicine

Table 3. Profile of biphasic anaphylaxis in Japanese inpatients (n = 7)

Age (years)	Sex	Antigen	Initial symptoms	Initial treatments	Time of recurrence (h)	Recurrent symptoms/severity	Additional treatments
4	M	Milk	Skin, GI	Epi, CS, H_1, H_2	2	Card/severe	None
1	M	Egg	Skin, Resp, Card	Epi, CS, H_1, H_2	3	Skin, Resp/mild	None
42	M	Fish	Skin, Resp, Card	Epi, CS, H_1, H_2	8	Skin, Resp/mild	None
6	F	Antibiotic	Skin, Resp, GI	Epi, CS, H_1, H_2	8	Skin, Resp/mild	None
57	F	Drug	Skin, Card	H_1, H_2	18	Skin, Card/similar	Epi, CS, H_1, H_2
38	F	Antibiotic	Skin, Resp	H_1, H_2	24	Skin, Resp/similar	Epi, CS, H_1, H_2
69	F	Bee	Skin, GI	CS, H_1, H_2	36	Skin, Resp/mild	None

Card, cardiac symptoms; CS, corticosteroid; Epi, epinephrine; GI, gastrointestinal symptoms; H_1, H_1-antagonist; H_2, H_2-antagonist; Resp, respiratory symptoms; similar, symptoms similar to initial reaction.

(85.4%), 7 (100%), and 4 (100%) cases of uniphasic, biphasic, and protracted reactions, respectively. The median times from onset to initial treatments were 60 min and 70 min in uniphasic and biphasic reactions. Tables 3 and 4 summarize biphasic reactions and protracted anaphylaxis, respectively.

The median onset time of biphasic reaction was 8 h. Dermatologic symptoms were mostly observed (6/7 cases). Regarding severity in biphasic reactions, mild symptoms were seen in 4 cases, reactions similar to initial symptoms were seen in 2 cases, and only 1 case was severe. The onset of a biphasic reaction after more than 8 h was seen in 3 cases. In these cases, epinephrine was not given. In 2 of the cases a steroid was not administered, either.

The duration of protracted anaphylaxis varied from 2 to 8 days, although only dermatologic symptoms were observed at the end of the treatment.

DISCUSSION

THE FIRST CASE report of biphasic anaphylaxis was described by Popa *et al.* in 1984,[8] although a biphasic anaphylactic reaction was reported by Duke in 1983.[9] Popa *et al.* reported that three patients redeveloped systemic anaphylactic symptoms. Stark *et al.* reported the first prospective evaluation of biphasic and protracted anaphylaxis in 1986.[10] Since then, several bodies of research have reported on the incidence and characteristics of biphasic anaphylactic reactions. To the best of our knowledge, this is the first study to investigate the incidence and characteristics of biphasic and protracted anaphylaxis in Japanese ED, although this study was carried out in an inpatient setting.

Recent reports have shown that the incidence of biphasic reactions ranges from 1 to 23%, the onset of recurrence of symptoms ranges from 1 to 78 h, and most secondary responses occur within 8 h after resolution of the first event.[4,5,11,12] In our results, the incidence was 6.1%, time of recurrence ranged from 2 to 36 h, and the median time of secondary reactions was 8 h. Regarding incidence, our results were not for all patients with anaphylaxis, but only for inpatients. We generally admitted patients with anaphylaxis to our hospital to monitor for a biphasic reaction. However, sometimes this was not possible because of the patients' circumstances. In such cases, we observed them in an ED for

Table 4. Profile of protracted anaphylaxis in Japanese inpatients (n = 4)

Age (years)	Sex	Antigen	Symptoms	Treatments	Duration (days)	Persistent symptoms	Additional treatments
27	F	Drug	Skin, Resp	Epi, CS, H_1, H_2	2	Card	CS, H_1
51	F	NSAIDs	Skin, Resp,	CS, H_1, H_2	3	Skin, Resp	CS, H_1, H_2
45	M	Shellfish	Skin, Resp, Card	Epi, CS, H_1, H_2	8	Skin, Resp	Epi (continual)
21	M	Buckwheat	Skin, Resp, Card, GI	Epi, CS, H_1, H_2	8	Skin, Resp	CS, H_1

Card, cardiac symptoms; CS, corticosteroid; Epi, epinephrine; GI, gastrointestinal symptoms; H_1, H_1-antagonist; H_2, H_2-antagonist; NSAIDs, non-steroidal anti-inflammatory drugs; Resp, respiratory symptoms.

© 2014 Japanese Association for Acute Medicine

4–10 h based on the severity of the initial symptoms and the patient's clinical course after treatment, and we made sure there was an environment with adequate supervision before discharging the patient to home. In total, we observed 139 patients who were not admitted to an ED, and none of them had biphasic reactions during that period of time.

The most common recurrent symptom was dermatologic reaction, followed by respiratory symptoms, similar to previous reports.[4,5,11,12] The severity of biphasic reactions were mostly mild but could have been fatal, as was found in most reports,[4,5,11,12] whereas mild reactions or those similar to the initial symptoms were observed in this study in all but one severe case.

Possible risk factors for biphasic reactions, such as current asthma, severe initial symptoms, delayed treatment, timing and dose of epinephrine and steroid administration, and delayed resolution of initial symptoms have been discussed.[4] However, there are few consistent risk factors that can be used to predict biphasic reactions,[4] although a recent study showed that older individuals and females require more than one dose of epinephrine, and low peak expiratory flow is a possible risk factor.[5,12]

Our treatment strategy for patients with anaphylaxis is as follows. First, we secure the airway, breathing, and circulation, and we perform intubation, administer oxygen, and fluid and pressor resuscitation if necessary. At the same time, we treat with epinephrine, then repeat it and administer continuously as needed. Second, we give corticosteroid, H1-antagonist, and H2-antagonist based on the severity of each case. Glucagon is another agent that we need to consider when a patient is taking a β-blocker. As current guidelines recommend, epinephrine should be injected immediately after diagnosing a patient with anaphylaxis.[13] However, we injected epinephrine in only 59.6% of cases in this study. If we had used epinephrine in each case, some biphasic reactions could have been prevented or these clinical courses would have been milder.

The hypotheses of biphasic anaphylactic pathogenesis have been discussed. It was originally thought that the recurrence of symptoms is not attributable to a true biphasic reaction but represents a recurrence of a temporarily interrupted protracted initial response attributable to appropriate but perhaps inadequate therapy.[10,14,15] A recent theory is that the late response is attributable to the activation of secondary inflammatory pathways, such as the complement system and the clotting and clot lysis pathways, resulting from mediators released during the initial event.[16,17]

The most important clinical point for emergency physicians is the observation period after successful treatment of an anaphylactic episode. According to some case reports, biphasic reactions occur up to 78 h after initial reactions.[18] There is no definitive answer, yet. However, we suggest that an 8-h and, ideally, a 24-h observation period is optimal based on these results and some other bodies of research.[4] We had only three patients with biphasic anaphylaxis whose onset of recurrence was over 8 h. These patients had mild or similar symptoms compared to their initial ones, and all of them recognized their reactions well. Regarding initial treatment, two of the patients did not receive steroids and none of the three patients received an epinephrine injection. If we had used epinephrine and steroids in each case, these clinical courses could have been controlled. Unfortunately, we could not obtain definitive clinical criteria identifying those patients who are at risk for biphasic reactions, so we focused on educating patients, environments with adequate supervision, and availability of an auto-injectable epinephrine to prevent the patients from being in critical condition.

Protracted reaction is another unique clinical course of patients with anaphylaxis. It was first described by Lockey *et al.* in 1974.[19] However, only a limited number of case reports and a small series are available.[6,20–22] In this study, the incidence of protracted reactions was only 4 in 114 cases (3.5%). As we observed in biphasic reactions, dermatologic and respiratory symptoms were mostly seen. The duration of protracted reactions was from 2 to 8 days, despite additional treatments. Protracted anaphylaxis also should be taken into account when emergency physicians take care of any patients with anaphylaxis.

Our study has several potential limitations. First, this was a retrospective study. We only evaluated anaphylaxis in inpatients, due to a lack of outpatient monitoring. We suspected that patients in this study were more severe because of the inpatient setting. If we had investigated every patient with anaphylaxis, including outpatients, this data would be more available. Second, we only observed patients for a minimum of 24 h. As stated earlier, biphasic reactions could occur up to 78 h after initial reactions, according to some case reports. Thus, we might have overlooked some biphasic anaphylaxis when reactions occurred after discharging patients to home. We also might have missed some reactions because of less careful observation. If we had checked every single symptom, and contacted every patient after discharging to home, this research would have been more precise. Third, this was a single-center study in a limited region in Japan. According to a report from a different facility in Japan, bees were a common antigen, followed by drugs.[23] In our study, the most common antigen overall for anaphylaxis was foods, followed by drugs. If this study had taken place in a different setting, anaphylactic clinical courses would have been different. Finally, we need to think of potential incidental confounding factors in addition to patient age and sex, due to the study setting.

© 2014 Japanese Association for Acute Medicine

CONCLUSIONS

IN THIS STUDY, the incidence of biphasic and protracted anaphylaxis was 6.1% and 3.5%, respectively. The median onset of biphasic reactions was 8 h, and most symptoms were mild or similar to the initial reaction. Epinephrine and steroids should be given to every patient with anaphylaxis, because these agents could potentially prevent biphasic reactions. We suggest that patients with anaphylaxis need an 8-h, and ideally a 24-h, observation period in order to monitor possible biphasic reactions. Regarding protracted anaphylaxis, duration was up to 8 days, although only dermatologic symptoms were observed at the end of the treatment.

CONFLICT OF INTEREST

NONE.

REFERENCES

1 Gaeta TJ, Clark S, Pelletier AJ *et al.* National study of US emergency department visits for acute allergic reactions, 1993 to 2004. Ann. Allergy Asthma Immunol. 2007; 98: 360–5.
2 Simons FE. Anaphylaxis. J. Allergy Clin. Immunol. 2010; 125: S161–81.
3 Lieberman P. Biphasic anaphylactic reactions. Ann. Allergy Asthma Immunol. 2005; 95: 217–26.
4 Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. Immunol. Allergy Clin. North Am. 2007; 27: 309–26.
5 Scranton SE, Gonzalez EG, Waibel KH. Incidence and characteristics of biphasic reactions after allergen immunotherapy. J. Allergy Clin. Immunol. 2009; 123: 493–8.
6 Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. J. Allergy Clin. Immunol. 1986; 78: 76–83.
7 Sampson HA, Munoz-Furlong A, Campbell RL *et al.* Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J. Allergy Clin. Immunol. 2006; 117: 391–7.
8 Duke WW. Allergy, Asthma, Hayfever, and Urticarial. New York: CV Mosby, 1925.
9 Portier P, Richet C. De I‘ action anaphylactique de certains venins. C Roy Soy Biol. (Paris) 1902; 54: 170. (In French.)
10 Popa VT, Lerner SA. Biphasic systemic anaphylactic reactions: three illustrative cases. Ann. Allergy 1984; 53: 151–5.
11 Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. Ann. Allergy Asthma Immunol. 2007; 98: 64–9.
12 Confino-Cohen R, Goldberg A. Allergen immunotherapy-induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective study. Ann. Allergy Asthma Immunol. 2010; 104: 73–8.
13 Kemp SF, Lockey RF, Simons FE, World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy 2008; 63: 1061–70.
14 Bleecker ER, Lichtenstein LM. Systemic anaphylaxis. In: Lichtenstein LM, Fauci AS (eds). Current Therapy in Allergy and Immunology. Philadelphia: BC Decker, 1983; 3–23.
15 Beall GN. Anaphylaxis. In: Beall GN (ed). Allergy and Clinical Immunology. New York: Wiley and Sons, 1983; 125.
16 Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Middleton E, Adkinson NF, Yunginger JW *et al.* (eds). Allergy: Principles and Practice, 6th edn. St. Louis: Mosby Year Book 2003.
17 De Souza RL, Short T, Warman GR *et al.* Anaphylaxis with associated fibrinolysis, reversed with tranexamic acid and demonstrated by thrombelastography. Anaesth. Intensive Care 2004; 32: 580–7.
18 Douglas DM, Sukenick E, Andrade WP *et al.* Biphasic systemic anaphylaxis: an inpatient and outpatient study. J. Allergy Clin. Immunol. 1994; 93: 977–85.
19 Lockey RF, Bukantz SC. Allergic emergencies. Med. Clin. North Am. 1974; 58: 147–56.
20 Vinuya RZ, Simon MR, Schwartz LB. Elevated serum tryptase levels in a patient with protracted anaphylaxis. Ann. Allergy 1994; 73: 232–4.
21 Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N. Engl. J. Med. 1992; 327: 380–4.
22 Limb SL, Starke PR, Lee CE *et al.* Delayed onset and protracted progression of anaphylaxis after omalizymab administration in patients with asthma. J. Allergy Clin. Immunol. 2007; 120: 1378–81.
23 Nobuki S, Shigehiro S, Satoko I *et al.* Anaphylaxis: a review of 302 cases in Iwate Prefectural Critical Care and Emergency Center. J. Jpn Assoc. Acute Med. 2010; 21: 282–92.

© 2014 Japanese Association for Acute Medicine